DOI:
10.1016/j.ajog.2019.09.040

Document Version
Peer reviewed version

MAVRIC: A Multicentre Randomised Controlled Trial of Transabdominal Versus Transvaginal Cervical Cerclage

Andrew Shennan, Manju Chandiramani, Phillip Bennett, Anna L. David, Joanna Girling, Alexandra Ridout, Mr Paul T. Seed, Nigel Simpson, Steven Thornton, Graham Tydeman, Siobhan Quenby, Jenny Carter

PII: S0002-9378(19)31206-2

DOI: https://doi.org/10.1016/j.ajog.2019.09.040

Reference: YMOB 12906

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 4 July 2019

Revised Date: 30 August 2019

Accepted Date: 16 September 2019

Please cite this article as: Shennan A, Chandiramani M, Bennett P, David AL, Girling J, Ridout A, Seed PT, Simpson N, Thornton S, Tydeman G, Quenby S, Carter J, MAVRIC: A Multicentre Randomised Controlled Trial of Transabdominal Versus Transvaginal Cervical Cerclage, *American Journal of Obstetrics and Gynecology* (2019), doi: https://doi.org/10.1016/j.ajog.2019.09.040.

MAVRIC: A Multicentre Randomised Controlled Trial of Transabdominal Versus Transvaginal Cervical Cerclage

Andrew SHENNAN[a], Manju CHANDIRAMANI[a], Phillip BENNETT[b], Anna L DAVID[c] Joanna GIRLING[d], Alexandra RIDOUT[a], Mr Paul T SEED[a], Nigel SIMPSON[e], Steven THORNTON[f], Graham TYDEMAN[g], Siobhan QUENBY[h], Jenny CARTER[a]

[a]Department of Women and Children's Health
School of Life Course Sciences, Faculty of Life Sciences and Medicine,
King's College London, London, SE1 7EH, UK

[b]Parturition Research Group
Institute of Reproductive and Development Biology,
Imperial College London, Du Cane Road, London W12 0NN, UK

[c]UCL EGA Institute for Women's Health
University College London,
Medical School Building,
74 Huntley Street, London WC1E 6AU

[d]Department of Obstetrics and Gynaecology
West Middlesex University Hospital,
Chelsea and Westminster Hospital NHS Foundation Trust
Twickenham Road, Middlesex TW7 6AF

[e]Department of Women's and Children's Health
University of Leeds
Worsley Building, Clarendon Way, Leeds LS2 9NL

[f]Barts and the London School of Medicine and Dentistry,
Queen Mary University of London. Charterhouse Square,
London EC1M 6BQ

[g]Forth Park Hospital, Fife
Hayfield House, Hayfield Road, Kirkcaldy, KY2 5AH

[h]Division of Biomedical Sciences, Warwick Medical School
University of Warwick, Coventry, UK

Corresponding Author:
Andrew Shennan
[a]Department of Women and Children's Health,
School of Life Course Sciences, Faculty of Life Sciences and Medicine,
King's College London, London, SE1 7EH, UK
Andrew.shennan@kcl.ac.uk
+447976822634

"Declaration of interests" (all authors)

None to declare.

Funding: The trial was registered with the WHO International Clinical Trials Registry Platform (ISRCTN33404560) and funded by J P Moulton Charitable Foundation (Registered Charity No. 1109891). PTS is partly funded by Tommy's (Registered charity no. 1060508) and by CLAHRC South London (NIHR).

Condensation: Abdominal cerclage was demonstrated to be superior to low vaginal cerclage in women with prior failed cerclage in preventing early preterm birth (<32 weeks) and fetal loss.

Short Title: MAVRIC: A Multicentre Randomised Controlled Trial of Transabdominal Versus Transvaginal Cervical Cerclage

Key words: Failed stitch, Recurrent late miscarriage, Transabdominal cerclage, Vaginal cerclage

AJOG at a Glance

Why was the study conducted?

Vaginal cerclage is recommended in women with evidence of cervical insufficiency, for example a history of multiple recurrent mid trimester losses or early preterm birth. When vaginal cerclage fails, transabdominal cerclage has been advocated, with observational studies suggesting higher rates of success. We searched PubMed for original articles published in English prior to September 2018 with the search terms “preterm birth OR cerclage OR transabdominal cerclage OR high vaginal cerclage”. There were no randomised studies that compared abdominal versus repeat vaginal cerclage.

What are the key findings?

This randomised controlled trial provides the first direct comparison of abdominal and high vaginal cerclage with low vaginal cerclage. Abdominal cerclage was demonstrated to be superior to low vaginal cerclage in women with prior failed cerclage in preventing early preterm birth (less than 32 weeks) and fetal loss. High vaginal cerclage was no better than low vaginal cerclage in preventing early birth.

What does this study add to what is already known?

Women with a prior failed vaginal cerclage (pregnancy delivered before 28 weeks of gestation) should be offered an abdominal cerclage, either before or in early pregnancy.

ABSTRACT

Background

Vaginal cerclage (a suture around the cervix) is commonly placed in women with recurrent pregnancy loss. These women may experience late miscarriage or extreme preterm delivery, despite being managed with cerclage. Transabdominal cerclage has been advocated following failed cerclage, although its efficacy is unproven by randomised controlled trial.

Objective

The objective of this study was to compare transabdominal cerclage or high vaginal cerclage to low vaginal cerclage in women with a history of failed cerclage. Our primary outcome was delivery before 32 completed weeks of pregnancy.

Study Design

This was a multicentre randomised controlled trial. Women were randomly assigned (1:1:1) to receive transabdominal cerclage, high vaginal cerclage or low vaginal cerclage, either prior to conception or before 14 weeks' gestation.

Results

111/139 women recruited who conceived were analysed: 39 to transabdominal cerclage, 39 to high vaginal cerclage and 33 to low vaginal cerclage. Rates of preterm birth <32 weeks were significantly lower in women who received transabdominal cerclage compared to low vaginal cerclage [8% (3/39) v 38% (15/39), RR 0.23 (95% CI 0.07 to 0.76), p=0.0078]. Number needed to treat to prevent one preterm birth was 3.9 (95% CI 2.2 to 13.3). There was no difference in preterm birth rates between high and low vaginal cerclage [38% (15/39) vs 33% (11/33), RR 1.15 (95% CI 0.62 to 2.16), p=0.81].

No neonatal deaths occurred. In an exploratory analysis, women with transabdominal cerclage had fewer fetal losses compared to low vaginal cerclage [3% (1/39) vs 21% (7/33), RR 0.12 (95% CI 0.016 to 0.93), p=0.02]. Number needed to treat to prevent one fetal loss was 5.3 (95% CI 2.9 to 26).

Conclusions

Transabdominal cerclage is the treatment of choice for women with failed vaginal cerclage. It is superior to low vaginal cerclage in reducing risk of early preterm birth and fetal loss in women with previous failed vaginal cerclage. High vaginal cerclage does not confer this benefit. Numbers needed to treat are sufficiently low to justify transabdominal surgery and caesarean delivery required in this select cohort.

BACKGROUND

Recurrent late miscarriage and early spontaneous preterm birth is often treated with vaginal cerclage (a suture placed around the cervix). This is known to have a significant benefit in a small number of cases probably representing those with genuine cervical incompetence, or who have traumatic cervical damage, such as that caused by surgery[1]. When evaluated by randomised controlled trial (RCT), vaginal cerclage (VC) has limited value, compared to conservative management (numbers needed to treat were 25)[2]. Even without cerclage, most women will have a successful subsequent pregnancy. The challenge is to identify those women whose pregnancy losses are genuinely due to cervical weakness; women who experience multiple late miscarriages or early spontaneous preterm births are more likely to fall into that category.

In women for whom vaginal cerclage fails, abdominal cerclage (TAC, inserted laparoscopically or via laparotomy) has been advocated but requires more extensive surgery than vaginal cerclage, and caesarean delivery. A number of observational series[3–6] have suggested that abdominal cerclage is highly successful, however abdominal cerclage has never been evaluated in an RCT.

We hypothesised that abdominal cerclage (TAC) would result in lower rates of late miscarriage and early preterm delivery compared to low vaginal cerclage (LVC) by maintaining structural and biochemical integrity of the cervix because it is placed higher in the cervix, ideally at the level of the internal os. This may prevent the infective/inflammatory cascade associated with cervical shortening[7], which may be due either to stretch of the fetal membranes as the internal os opens[8], or loss of the cervical barrier to ascending infection[7]. A VC can also be placed higher in the cervix, by mobilising the bladder (HVC). It is unknown whether this also results in lower rates of late miscarriage or PTB when compared to LVC.

METHODS

Study design and participants

The MAVRIC trial was a multicentre RCT funded by the J P Moulton Charitable Foundation and supported by the NIHR Clinical Research Network (CRN). NHS Research Ethical Committee approval was obtained (REC 07/H1102/113) and the trial was registered on the International Standard Randomised Controlled Trial Registry (ISRCTN33404560).

Women were eligible for trial inclusion if they had a history of spontaneous late miscarriage or preterm birth between 14 and 28 completed weeks of pregnancy with low vaginal cerclage (LVC) in situ, but excluding rescue cerclage procedures, i.e. cerclage inserted with exposed membranes. Women were eligible for randomisation pre-conceptually or at less than 14 weeks' gestation. Only data from the first pregnancy following randomisation was analysed (figure 1).

Participants were referred from hospitals across the United Kingdom and recruited at 9 sites (London (4 sites), Kirkcaldy, Sunderland, Newcastle, Bradford and Edinburgh) between January 2008 and September 2014. All participants gave written informed consent and were over the age of 16.

Procedures

Women with a previous failed cerclage were randomised to one of the following:

1. TAC: Transabdominal cerclage
2. HVC: High vaginal cerclage
3. LVC: Low vaginal cerclage

Techniques used were left to the local clinician's discretion. Details of surgical and anaesthetic technique were collected (table 6). All procedures were carried out by a consultant level surgeon (table 7). Vaginal cerclage was inserted prior to 16 weeks' under regional anaesthetic and removed at 37 weeks' gestation, or earlier if preterm labour ensued. HVC involved mobilisation of the bladder from the anterior cervix allowing the suture to be placed higher, and usually required regional anaesthetic for removal. TAC was placed pre-conceptually or before 14 weeks' gestation as an open procedure under either regional or general anaesthetic, requiring inpatient stay of up to 3 days. Women with TAC were scheduled for delivery by elective caesarean section at 38 to 39 weeks, with retention of the TAC for future pregnancies.

Randomisation and masking

Women enrolled in MAVRIC were randomly assigned to TAC, HVC or LVC (1:1:1) using a computer-generated randomisation procedure incorporated in an internet-based secure trial database (www.medscinet.net/MAVRIC). Minimisation was used to balance two prognostic variables: pregnancy at time of randomisation and gestational age of previous late miscarriage or preterm delivery (Table 1). Due to the nature of the interventions, treatment allocation was known to both participants and health care professionals. Written informed consent was obtained from all participants and baseline demographic characteristics, risk factors and obstetric and gynaecologic history were entered into the study specific database.

Cerclage insertion was performed electively between 10 to 16 weeks' (14 weeks for TAC) or pre-conception if assigned to TAC or HVC, according to clinician and patient preference. All LVCs were carried out at the women's local maternity unit. As HVCs and TACs are more specialist procedures, these were carried out in one of the designated centres, to ensure a suitably experienced surgeon completed the procedure. Following cerclage insertion, women were monitored and managed according to local clinicians' practice. All care was in line with contemporaneous evidence-based guidelines.

Outcomes

Our primary outcome on which the trial was powered was delivery before 32 completed weeks of pregnancy. Pre-defined secondary outcomes included neonatal death, serious operative complication rates and complications of pre- and post-conception cerclage (HVC and TAC).

Pregnancy outcomes were obtained from case note review, by trained research midwives. Women were considered to have had a spontaneous preterm birth (sPTB) if they had spontaneous onset of labour, or experienced preterm rupture of membranes and delivered prematurely, regardless of mode of delivery. There were no changes to pre-specified outcomes during recruitment. All pre-specified analyses were undertaken.

As there were no neonatal deaths, we performed an additional analysis by comparing the overall fetal loss rate by trial arm (composite of late miscarriage and stillbirth).

Sample size calculation

Sample size estimation was informed by data from an observational study by Davis *et al*. (4), the best available evidence at the time. Our primary outcome was rate of delivery before 32 complete weeks of gestation. Assuming a baseline event rate of 38% with LVC and 10% with TAC (4), a total of 43 women in each of the three groups (TAC, HVC and LVC) was required for 80% power, at the 5% significance level (2-tailed), to show a significant difference between LVC and the other two groups (effect of 28% absolute risk reduction). Given this was a feasibility trial we made no adjustments for multiple testing.

Statistical analysis

Statistical analyses were undertaken in Stata version 14·2 (StataCorp 15.1, College Station, Texas). Analysis was by modified intention-to-treat, with planned comparison of treatment effects for binary endpoints using risk ratios and significance tests for both primary and secondary endpoints. The modification was to take into account patients who did not conceive post-randomisation. A vaginal cerclage is unlikely to be considered in a non-pregnant patient and therefore these women were removed to ensure the analysis remained clinically valid. We also performed a per protocol analysis, although this was not predefined.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Participants

This was a multicentre RCT, with patients as the unit of randomisation. The full study protocol can be found on the King's College London website (https://www.kcl.ac.uk/lsm/research/divisions/wh/clinical/open/mavric.aspx).

139 participants were recruited and randomly allocated a treatment. The first patient was recruited in January 2008. Recruitment ended in September 2014, when the planned recruitment target (n=129) had been exceeded. Seventy-nine women were not pregnant at the time of randomisation, which was a higher number than

anticipated. At this time 104 women had conceived. Four years later, only 7 additional women had conceived and delivered (1 in 2014, 4 in 2015 and 2 in 2017). Despite extensive efforts, we were unable to trace the outcomes of two participants who were known to have moved abroad.

The data monitoring committee was consulted in September 2018; there had been no further conceptions during the preceding 12 months, and therefore the decision was made to proceed with analysis on 111 women. Only data from the next pregnancy following randomisation was analysed (Figure 1).

Of the 111 participants who had conceived and with known outcome, 39 were randomised to TAC, 39 to HVC and 33 to LVC. All first trimester miscarriages (less than 13 weeks') post randomisation were excluded from the analysis (3 excluded: 1 in TAC, 1 in HVC and 1 in LVC group). Almost half (49%, 19/39) of TACs were placed pre-conception; all of the HVC and LVC were placed prior to 16 weeks' gestation.

Baseline demographic characteristics are shown in Table 2. The median gestation of failed cerclage was 22 weeks (IQR 20 to 24). Our inclusion criteria defined cerclage failure as preterm delivery before 28 weeks, however 69% (96/139) of women had a failed cerclage that resulted in late miscarriage (<24 weeks). 97%, 95% and 91% of each randomised group had 2 or more late second trimester losses (95% of the whole group, 105/111). Most others had cervical shortening detected during screening for a prior preterm loss.

Patients were managed as per local clinical practices: 17% (6/36) of women allocated to TAC were also prescribed progesterone, 28% (10/36) with HVC and 48% (14/29) with LVC. All women had a history of recurrent early delivery: the median number of late miscarriages was 2 (IQR 1 to 5) and preterm births were 1 (IQR 0 to 5).

Outcomes

There was a statistically significant reduction in preterm birth less than 32 completed weeks' gestational age (the primary outcome) in women allocated to TAC compared to LVC [8% (3/39) v 38% (15/39), RR 0□23 (95% CI 0□07 to 0□76) p=0□0078]. There were no iatrogenic preterm deliveries among these women. Number needed to treat (NNT) to prevent one sPTB was 3.9 (95% CI 2□2 to 13□3). There was no difference in rates of sPTB between high and low VC [38% (15/39) vs 33% (11/33), RR 1□15 (95% CI 0□62 to 2□16), p=0□81].

TAC also demonstrated benefit when compared to HVC [8% (3/39) v 38% (15/39), RR 0□2 (95% CI 0□063 to 0□64), p=0□0024]. NNT was 3□2 (95% CI 2□0 to 7□4) (see Figure 2).

No neonatal deaths occurred. Women with a TAC had fewer fetal losses (late miscarriage or stillbirth), compared to LVC [3% (1/39) vs 21% (7/33), RR 0□12 (95% CI 0□016 to 0□93), p=0□02]. NNT to prevent one fetal loss was 5□3 (95% CI 2□9 to 26).

Serious adverse events (pre-defined as per protocol) were reported in four cases (2 x cervical tears, 1 x ITU admission with sepsis and 1 case of cardiomyopathy), all of which occurred in women with high (n=3) or low (n=1) vaginal cerclage. 6 women received a subsequent rescue cerclage (4 who were allocated HVC, 2 who were allocated LVC). The indication for rescue cerclage was painless dilatation identified during routine preterm birth surveillance assessments (data only available for 3/6 women). Table 6 gives surgical and anaesthetic details for each procedure divided by outcome; no specific trends are apparent, and techniques are equally spread across the outcome groups.

72% (28/39) of women with a TAC *in situ* delivered at term, compared to fewer than half of women with HVC (46%, 18/39) or LVC (48%, 16/33) (Table 4).

Eight women did not receive treatment as per allocation (see Table 5), as a result of patient choice following randomisation or treatment allocation being judged inappropriate, for example, the cervix was found to be too short on vaginal examination at time of procedure. Results are presented by intention to treat however, as shown in Table 8, were similar when analysed as per protocol.

DISCUSSION

Principal Findings

This is the first RCT comparing abdominal cerclage with vaginal cerclage. Our findings show that transabdominal cerclage is superior to low vaginal cerclage in preventing early PTB for women with an unsuccessful previous vaginal cerclage pregnancy. Compared to LVC, there was no benefit of HVC. In addition, transabdominal cerclage was superior to low vaginal cerclage in preventing fetal loss (late miscarriage and stillbirth).

Clinical Implications

Numbers needed to treat were modest to both prevent delivery before 32 weeks (<4) and to prevent fetal loss (<6), and therefore the uptake of this procedure is likely to be efficient and cost effective. Further work should establish the health economic impact of such procedures including the longer-term need for caesarean sections and associated morbidity.

Strengths and limitations

Although our numbers were small, they were based on an anticipated large treatment effect and we achieved the assumed event rates in our protocol, suggesting our findings are unlikely to be subject to a type 1 error. We had crossovers during the trial, but fewer than 10% of participants (8/111), and following a post-hoc per protocol analysis, the treatment effect was greater in favour of abdominal cerclage.

Women with a history of failed cerclage are rare. It is challenging to randomise such women into a trial where there are strong prior beliefs as to the perceived risk or benefit of the intervention and, therefore, lack of equipoise. This explains the length of time needed to reach the recruitment target, in spite of the national multicentre trial design. We found clinicians reluctant to randomise, with many unwilling to perform, and others unwilling to withhold an abdominal cerclage, even in the context of a trial. In addition, women who have experienced multiple pregnancy losses have often extensively researched the treatment options and have a fixed idea of which intervention would be best for them, so are unwilling to be randomised. We were unable to collect accurate screening data due to the referral nature of the trial.

The trial was underpowered to evaluate safety concerns and meaningful subgroup analysis was not possible. Absolute numbers of women with prior cervical surgery, history of UTI or BV do differ slightly between arms but as per the CONSORT guidance, it is not recommended to carry out comparisons of randomised differences as these are likely the result of chance rather than bias, and can be misleading (9). Additionally we were unable to analyse complications pre- and post-conception with the abdominal procedure due to their rarity (none) and small numbers. No clinicians used laparoscopic TAC procedures and we therefore could not evaluate possible differences between this and other techniques, such as types of sutures. Other concerns related to abdominal cerclage include managing early miscarriage and infertility, were not apparent in this study. It is our experience,

however, that evacuation of the uterus for missed miscarriage, or termination of pregnancy for fetal abnormality can be safely performed up to 14 weeks, leaving the abdominal cerclage in place.

Although the trial intended to evaluate rates of neonatal death, there were none. This suggests that women with a prior failed pregnancy before 28 weeks tend to have fetal losses at pre-viable gestations in the second trimester, if they recur. The mechanism of pregnancy failure causing late miscarriage and early preterm birth (resulting in neonatal death) is likely to be the same, and as we excluded early miscarriage, we therefore believe our fetal loss rates are a meaningful comparator across treatments, although not predefined.

Comparison between TAC and HVC was not originally planned because we were investigating an improvement in preterm birth rates compared to standard practice, which at that time was LVC. Given the strong reduction in the rate of preterm birth in women with a TAC in situ, and the similarity between the groups with HVC and LVC, it was considered appropriate to also compare TAC with HVC. TAC was shown to strongly reduce preterm birth before 32 weeks compared to HVC as well as LVC. These results remained highly significant even after correcting for multiple testing using the Bonferroni correction (TAC v LVC, p=0.02, TAC v HVC, p=0.007).

The mechanism of benefit is not clear, but our findings suggest that an abdominally placed cerclage may prevent the initiation of contractions. A previous study suggested that the higher the vaginal cervical cerclage is placed, the lower the risk of preterm birth (10) but this was in a more heterogeneous, lower risk population. In the very high-risk cohort of the present study, high vaginal cerclage was no better. The multiple and varied risk factors in the abdominal cerclage group suggests the treatment effect is unrelated to aetiology.

Research Implications

Severe complications were rare but those that did occur were in women with a vaginal procedure. Three of the four were related to cerclage failure, including cervical trauma at early birth, and sepsis. Multiple abdominal procedures associated with the abdominal cerclage may ultimately cause more longer-term morbidity and we were unable to evaluate this within this study. Future research should define longer-term morbidity associated with the procedure (e.g. pelvic pain, repeat surgery) alongside a health economic evaluation of the procedure and its outcomes over a woman's reproductive life, but should include the reduced morbidity associated with fewer failed pregnancies.

Conclusions

While further research is needed to confirm the value of TAC in other high-risk groups, our findings suggest it is likely to be beneficial to women with previous failed vaginal cerclage. Implications for practice include the need to increase the availability of transabdominal cerclage for suitable women, and the training of obstetricians in this uncommon practice. The procedure is not technically difficult and most gynaecologists who undertake any form of pelvic surgery should be equipped with the fundamental skills.

Contributors

AS conceived the idea and is the guarantor. All the authors were involved in the design, collection, analysis, and interpretation of the data, the writing and critical review of the manuscript, and the decision to submit the manuscript for publication. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

This trial is registered with ISCRTRN Controlled Trials registry, ISCRTN89971375.

Disclaimer

This research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centres at Guy's and St Thomas' NHS Foundation Trust and King's College London, and University College London Hospitals. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

333

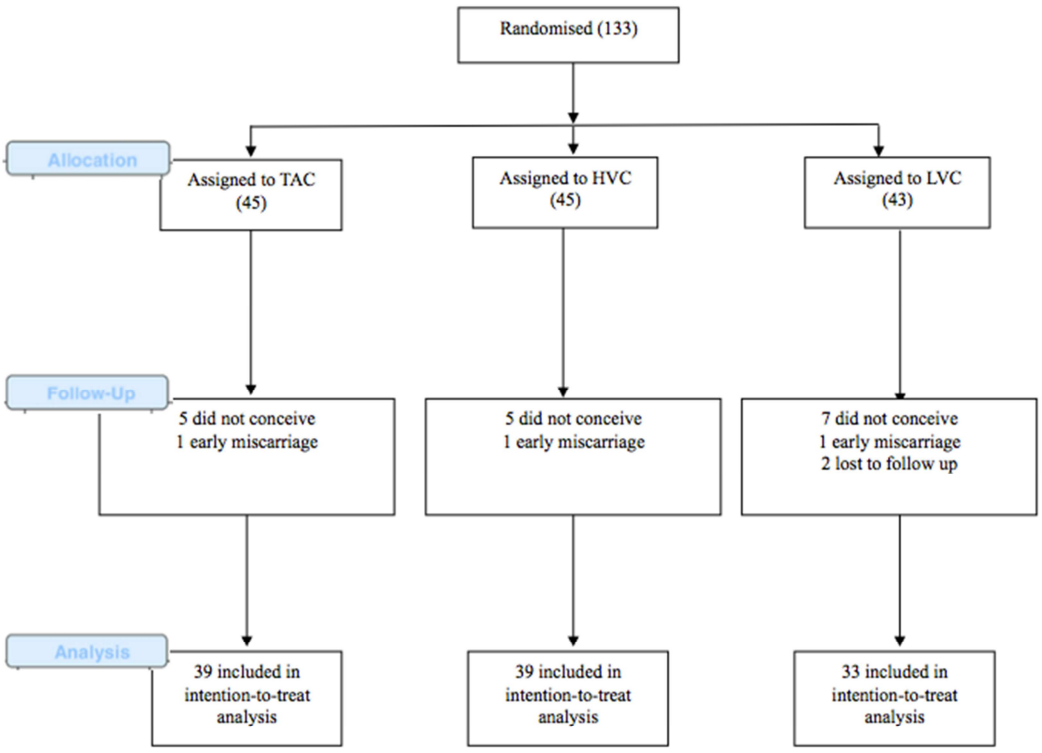
334

335

336 **FIGURES AND TABLES**

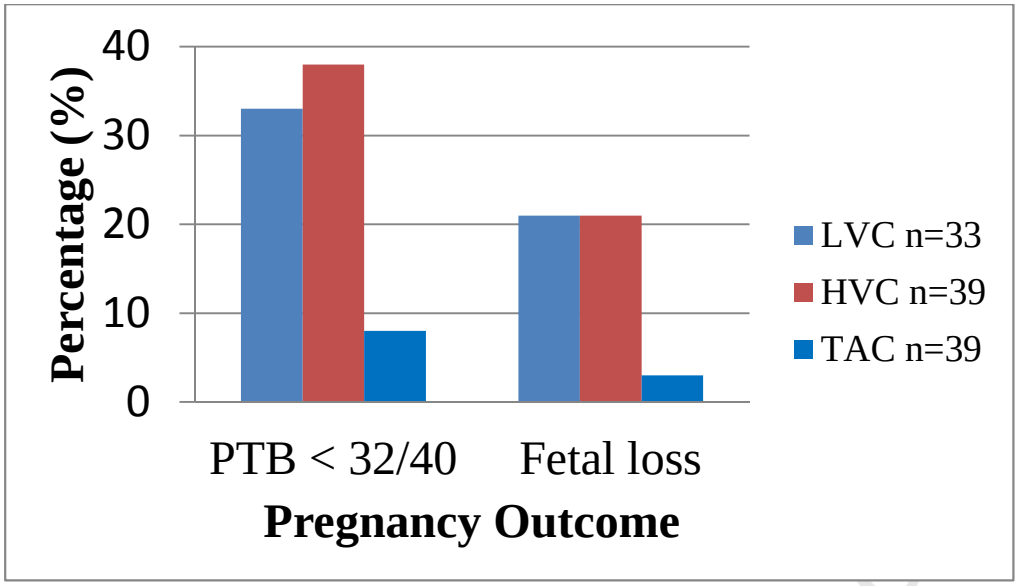
337 **Figure 1: Participant flow chart with treatment allocation and exclusions**

338



339

340 **Figure 2: Pregnancy outcome by treatment allocation**



341

342

343 **Table 1: Variables used for minimisation by trial allocation following exclusions**

	Transabdominal cerclage (39) n (%)	High vaginal cerclage (39) n (%)	Low vaginal cerclage (33) n (%)
Pregnant at randomisation	20 (44□4%)	16 (35□6%)	15 (34□9%)
Delivery before 24 weeks' in preceding pregnancy	31 (68□9%)	26 (57□8%)	29 (67□4%)

344

Treatment allocation	Transabdominal (N=39)	High vaginal (n=39)	Low vaginal (n=33)	All (n=111)
	Mean *(SD)*	Mean *(SD)*	Mean *(SD)*	Mean *(SD)*
Age at time of consent (years)	31□9 (5□1)	32□1 (5□3)	31□8 (5□1)	32□3 (5□4)
BMI (kg/m2)	29□9 (6□9)	30□1 (7□0)	29□9 (6□9)	30□1 (7□0)
Social class/occupation	n (%)	n (%)	n (%)	n (%)

Managerial/professional	12 (31%)	17 (44%)	13 (39%)	42 (38%)
Intermediate	20 (51%)	18 (46%)	14 (42%)	52 (47%)
Routine/unemployed	7 (18%)	4 (10%)	6 (18%)	17 (15%)
Ethnicity				
White	11 (28%)	10 (26%)	12 (36%)	33 (30%)
Black	21 (54%)	23 (59%)	18 (55%)	62 (56%)
Asian	4 (10%)	5 (13%)	3 (9%)	12 (11%)
Other	3 (8%)	1 (3%)	0 (0%)	4 (4%)

345 **Table 2: Maternal baseline demographic characteristics**

346

347 **Table 3: Cohort risk factors for spontaneous preterm birth by treatment allocation**

Risk Factors	**Transabdominal (n=39)**	**High vaginal (n=39)**	**Low vaginal (n=33)**	**All (n=111)**
Cervical surgery	2 (5%)	6 (15%)	9 (27%)	17 (15%)
Number of late miscarriages (mean, SD) Range	2□12 (1□15) 0 - 5	1□70 (1□12) 0 - 4	1□97 (1□08) 0 - 5	1□99 (1□15) 1 to 5
Number of early delivery (late miscarriage / PTB <28wks) (mean, SD)	2□73 (1□12)	2□65 (1□03)	2□91 (1□27)	2□76 (1□13)
2 or more second trimester losses (%, n)	97% (38/39)	95% (37/39)	91% (30/33)	95% (105/111)
Congenital Uterine Anomaly	3 (8%)	4 (10%)	3 (9%)	10 (9%)

Antiphospholipid syndrome (anticardiolipin or lupus anticoagulant)	1 (3%)	2 (5%)	0 (0%)	3 (3%)
Smoked during pregnancy	3(8%)	1(3%)	4 (12%)	8 (7%)
Past or present history of:				
Recurrent UTIs (>2) in pregnancy	3(8%)	4 (10%)	7 (21%)	14 (13%)
Group B Streptococcus	11 (28%)	10 (26%)	3(9%)	24 (22%)
Bacterial Vaginosis	3(8%)	4 (10%)	4 (12%)	11 (10%)
Recreational drug use	1(3%)	0 (0%)	2 (6%)	3 (3%)
Domestic Violence	0(0%)	0 (0%)	0 (0%)	0 (0%)

348

349

350 **Table 4: Pregnancy outcome by randomised allocation**

Treatment allocation	**Transabdominal (n=39)**	**High vaginal (n=39)**	**Low vaginal (n=33)**
Preterm (<32 weeks)*	3 (8%)	15 (38%)	11 (33%)
Preterm (<34 weeks)	4 (10%)	18 (46%)	13 (39%)
Preterm (<37 weeks)	11 (28%)	21 (54%)	17 (52%)
**primary outcome*			
Live birth	38 (92%)	31 (79%)	26 (79%)
Late Miscarriage	1 (3%)	7 (18%)	7 (21%)
Stillbirth	0 (0%)	1 (3%)	0 (0%)

All fetal losses	1 (3%)	8 (21%)	7 (21%)

***primary outcome**

Table 5: Details of patient crossovers from randomised allocation to treatment received

ID	Randomisation	Final procedure	Gestation - details	Outcome
24	LVC	TAC	At 10^{+0} – patient preference	39^{+1}
56	LVC	TAC	Preconception - patient choice	36^{+0}
66	LVC	HVC	At 14^{+0} – patient preference	37^{+5}
79	HVC	TAC	At 12^{+5} – patient preference	38^{+6}
87	TAC	LVC	At 10^{+6} – patient preference	38^{+0}
88	LVC	TAC	10^{+2} - No vaginal cervix on digital examination	37^{+6}
111	TAC	HVC	13^{+3} - patient request	38^{+5}
133	LVC	HVC	13^{+0} – transfer of care	38^{+2}

Table 6: Details of surgical and anaesthetic techniques

Procedure techniques	Transabdominal cerclage (N=39)		High vaginal cerclage (n=39)		Low vaginal cerclage (n=33)	
	sPTB <32/40 (n=3)	**Del >32/40 (n=36)**	**sPTB <32/40 (n=15)**	**Del >32/40 (n=24)**	**sPTB <32/40 (n=11)**	**Del >32/40 (n=22)**
Regional Anaesthesia	0/3 (0%)	6/33 (18%)	14/15 (93%)	20/23 (87%)	11/11 (100%)	13/16 (81%)

Mersiline Tape*	1/3 (33%)	4/28 (14%)	12/13 (92%)	21/22 (95%)	9/10 (90%)	16/17 (94%)
>=2 sutures inserted**	2/3 (66%)	18/28 (64%)	0/13 (0%)	1/22 (5%)	0/9 (0%)	0/17 (0%)
Cerclage tied anteriorly	0/3 (0%)	4/28 (14%)	13/13 (100%)	20/21 (95%)	10/10 (100%)	12/15 (80%)
Cerclage placed pre-conception	2/3 (66%)	18/36 (50%)	0/15 (0%)	0/24 (0%)	0/11 (0%)	0/22 (0%)
Subsequent rescue cerclage	0/3 (0%)	0/36 (0%)	3/15 (20%)	1/24 (4%)	2/11 (18%)	0/22 (0%)

***all other sutures were performed using monofilament suture **inserted simultaneously at the time of procedure**

Table 7: Operative details per randomisation arm

PTB <32/40	TAC (n=39)	HVC (n=39)	LVC (n=33)
Consultant grade surgeon	100%	100%	100%
Number of surgeons	7	4	7
Blood loss (median, IQR)	100 (50 to 150)	35 (20 to 60)	5 (5 to 20)
Operative time* (mins) (median, IQR)	42 (30 to 50)	13.5 (10 to 15)	25 (20 to 32)
Rate of PTB <32/40			
Overall	8% (3/39)	38% (15/39)	33% (11/39)
Primary surgeon	4% (1/25)	30% (10/33)	32% (8/25)
Other surgeons	15% (2/13)	60% (4/6)	50% (4/8)
Concurrent progesterone	17% (6/36)	28% (10/36)	48% (14/29)
Rescue cerclage	0% (0/39)	10% (4/39)	6% (2/33)

***start of operation to completion**

Table 8: Primary outcomes by intention to treat and as per protocol analysis

	Preterm birth < 32 weeks		Fetal loss	
	Intention to treat analysis	**As per protocol analysis**	**Intention to treat analysis**	**As per protocol analysis**

TAC versus LVC				
RR	0□23 (0□07 to 0□76) p=0□0078	0□21 (0□65 to 0□70) p=0□0059	0□12 (0□016 to 0□93) p=0□02	0□11 (0□014 to 0□86) p=0□018
TAC versus HVC				
RR	0□2 (0□063 to 0□64) p=0□0024	0□19 (0□058 to 0□59) p=0□001	0□13 (0□016 to 0□95) p=0□029	0□12 (0□015 to 0□88) p=0□012
HVC versus LVC				
RR	1□15 (0□62 to 2□16) p=0□81	1□15 (0□62 to 2□13) p=0□80	0□97 (0□39 to 2□38) p=1□00	0□96 (0□39 to 2□36) p=1□00

REFERENCES

1. Drakeley AJ, Roberts D, Alfirevic Z. Cervical stitch (cerclage) for preventing pregnancy loss in women. Cochrane Database Syst Rev. 2003;
2. Owen J, Hankins G, Iams JD, Berghella V, Sheffield JS, Perez-Delboy A, et al. Multicenter randomized trial of cerclage for preterm birth prevention in high-risk women with shortened midtrimester cervical length. Obstetrical and Gynecological Survey. 2010.
3. Dawood F, Farquharson R. Female Genital Tract Congenital Malformations. 2015;169–74. Available from: http://link.springer.com/10.1007/978-1-4471-5146-3
4. Davis G, Berghella V, Talucci M, Wapner RJ. Patients with a prior failed transvaginal cerclage: A comparison of obstetric outcomes with either transabdominal or transvaginal cerclage. Am J Obstet Gynecol. 2000;
5. Umstad MP, Quinn MA, Ades A. Transabdominal cervical cerclage. Aust New Zeal J Obstet Gynaecol. 2010;
6. Debbs RH, DeLa Vega GA, Pearson S, Sehdev H, Marchiano D, Ludmir J. Transabdominal cerclage after comprehensive evaluation of women with previous unsuccessful transvaginal cerclage. Am J Obstet Gynecol. 2007;
7. Iams JD, Goldenberg RL, Mercer BM, Moawad a, Thom E, Meis PJ, et al. The Preterm Prediction Study: recurrence risk of spontaneous preterm birth. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 1998;
8. Mohan AR, Sooranna SR, Lindstrom TM, Johnson MR, Bennett PR. The effect of mechanical stretch on cyclooxygenase type 2 expression and activator protein-1 and nuclear factor-κB activity in human amnion cells. Endocrinology. 2007;
9. Bland JM, Altman DG. Comparisons within randomised groups can be very misleading. BMJ. 2011;

10. Cook JR, Chatfield S, Chandiramani M, Kindinger L, Cacciatore S, Sykes L, et al. Cerclage position, cervical length and preterm delivery in women undergoing ultrasound indicated cervical cerclage: A retrospective cohort study. PLoS One. 2017;

Table 1: Variables used for minimisation by trial allocation following exclusions

	Transabdominal cerclage (39) **n (%)**	**High vaginal cerclage (39)** **n (%)**	**Low vaginal cerclage (33)** **n (%)**
Pregnant at randomisation	20 (44□4%)	16 (35□6%)	15 (34□9%)
Delivery before 24 weeks' in preceding pregnancy	31 (68□9%)	26 (57□8%)	29 (67□4%)

Table 2: Maternal baseline demographic characteristics

Treatment allocation	**Transabdominal (N=39)**	**High vaginal (n=39)**	**Low vaginal (n=33)**	**All (n=111)**
	Mean *(SD)*	Mean *(SD)*	Mean *(SD)*	Mean *(SD)*
Age at time of consent (years)	31□9 *(5□1)*	32□1 *(5□3)*	31□8 *(5□1)*	32□3 *(5□4)*
BMI (kg/m2)	29□9 *(6□9)*	30□1 *(7□0)*	29□9 *(6□9)*	30□1 *(7□0)*
Social class/occupation	n (%)	n (%)	n (%)	n (%)
Managerial/professional	12 (31%)	17 (44%)	13 (39%)	42 (38%)
Intermediate	20 (51%)	18 (46%)	14 (42%)	52 (47%)
Routine/unemployed	7 (18%)	4 (10%)	6 (18%)	17 (15%)
Ethnicity				
White	11 (28%)	10 (26%)	12 (36%)	33 (30%)
Black	21 (54%)	23 (59%)	18 (55%)	62 (56%)
Asian	4 (10%)	5 (13%)	3 (9%)	12 (11%)
Other	3 (8%)	1 (3%)	0 (0%)	4 (4%)

Table 3: Cohort risk factors for spontaneous preterm birth by treatment allocation

Risk Factors	**Transabdominal (n=39)**	**High vaginal (n=39)**	**Low vaginal (n=33)**	**All (n=111)**
Cervical surgery	2 (5%)	6 (15%)	9 (27%)	17 (15%)
History of late miscarriage (mean, SD) Range	2□12 (1□15) 0 - 5	1□70 (1□12) 0 - 4	1□97 (1□08) 0 - 5	1□99 (1□15) 1 to 5
History of early delivery (late miscarriage / PTB) (mean, SD)	2□73 (1□12)	2□65 (1□03)	2□91 (1□27)	2□76 (1□13)
Uterine anomaly	3 (8%)	4 (10%)	3 (9%)	10 (9%)
Antiphospholipid syndrome (anticardiolipin or lupus anticoagulant)	1 (3%)	2 (5%)	0 (0%)	3 (3%)
Smoked during pregnancy	3 (8%)	1 (3%)	4 (12%)	8 (7%)
Past or present history of:				
Recurrent UTIs (>2) in pregnancy	3 (8%)	4 (10%)	7 (21%)	14 (13%)
Group B Streptococcus	11 (28%)	10 (26%)	3 (9%)	24 (22%)
Bacterial Vaginosis	3 (8%)	4 (10%)	4 (12%)	11 (10%)

Recreational drug use	1 (3%)	0 (0%)	2 (6%)	3 (3%)
Domestic Violence	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 4: Pregnancy outcome by randomised allocation

Treatment allocation	**Transabdominal (n=39)**	**High vaginal (n=39)**	**Low vaginal (n=33)**
Preterm (<32 weeks)*	3 (8%)	15 (38%)	11 (33%)
Preterm (<34 weeks)	4 (10%)	18 (46%)	13 (39%)
Preterm (<37 weeks)	11 (28%)	21 (54%)	17 (52%)
**primary outcome*			
Live birth	38 (92%)	31 (79%)	26 (79%)
Late Miscarriage	1 (3%)	7 (18%)	7 (21%)
Stillbirth	0 (0%)	1 (3%)	0 (0%)
All fetal losses	1 (3%)	8 (21%)	7 (21%)

***primary outcome**

Table 5: Details of patient crossovers from randomised allocation to treatment received

ID	Randomisation	Final procedure	Gestation - details	Outcome
24	LVC	TAC	At 10^{+0} – patient preference	39^{+1}
56	LVC	TAC	Preconception - patient choice	36^{+0}
66	LVC	HVC	At 14^{+0} – patient preference	37^{+5}
79	HVC	TAC	At 12^{+5} – patient preference	38^{+6}
87	TAC	LVC	At 10^{+6} – patient preference	38^{+0}
88	LVC	TAC	10^{+2} - No vaginal cervix on digital examination	37^{+6}
111	TAC	HVC	13^{+3} - patient request	38^{+5}
133	LVC	HVC	13^{+0} – transfer of care	38^{+2}

Table 6: Details of surgical and anaesthetic techniques

Procedure techniques	Transabdominal cerclage (N=39)		High vaginal cerclage (n=39)		Low vaginal cerclage (n=33)	
	sPTB <32/40 (n=3)	**Del >32/40 (n=36)**	**sPTB <32/40 (n=15)**	**Del >32/40 (n=24)**	**sPTB <32/40 (n=11)**	**Del >32/40 (n=22)**
Regional Anaesthesia	0/3 (0%)	6/33 (18%)	14/15 (93%)	20/23 (87%)	11/11 (100%)	13/16 (81%)
Mersiline Tape*	1/3 (33%)	4/28 (14%)	12/13 (92%)	21/22 (95%)	9/10 (90%)	16/17 (94%)
>=2 sutures inserted**	2/3 (66%)	18/28 (64%)	0/13 (0%)	1/22 (5%)	0/9 (0%)	0/17 (0%)
Cerclage tied anteriorly	0/3 (0%)	4/28 (14%)	13/13 (100%)	20/21 (95%)	10/10 (100%)	12/15 (80%)
Cerclage placed pre-conception	2/3 (66%)	18/36 (50%)	0/15 (0%)	0/24 (0%)	0/11 (0%)	0/22 (0%)
Subsequent rescue cerclage	0/3 (0%)	0/36 (0%)	3/15 (20%)	1/24 (4%)	2/11 (18%)	0/22 (0%)

***all other sutures were performed using monofilament suture **inserted simultaneously at the time of procedure**

Table 7: Operative details per randomisation arm

PTB <32/40	TAC (n=39)	HVC (n=39)	LVC (n=33)
Consultant grade surgeon	100%	100%	100%
Number of surgeons	7	4	7
Blood loss (median, IQR)	100 (50 to 150)	35 (20 to 60)	5 (5 to 20)
Operative time* (mins) (median, IQR)	42 (30 to 50)	13.5 (10 to 15)	25 (20 to 32)
Rate of PTB <32/40			
Overall	8% (3/39)	38% (15/39)	33% (11/39)
Primary surgeon	4% (1/25)	30% (10/33)	32% (8/25)
Other surgeons	15% (2/13)	60% (4/6)	50% (4/8)
Concurrent progesterone	17% (6/36)	28% (10/36)	48% (14/29)
Rescue cerclage	0% (0/39)	10% (4/39)	6% (2/33)

***start of operation to completion**

Table 8: Primary outcomes by intention to treat and as per protocol analysis

	Preterm birth < 32 weeks		Fetal loss	
	Intention to treat analysis	**As per protocol analysis**	**Intention to treat analysis**	**As per protocol analysis**
TAC versus LVC				
RR	0□23 (0□07 to 0□76) p=0□0078	0□21 (0□65 to 0□70) p=0□0059	0□12 (0□016 to 0□93) p=0□02	0□11 (0□014 to 0□86) p=0□018
TAC versus HVC				
RR	0□2 (0□063 to 0□64) p=0□0024	0□19 (0□058 to 0□59) p=0□001	0□13 (0□016 to 0□95) p=0□029	0□12 (0□015 to 0□88) p=0□012
HVC versus LVC				
RR	1□15 (0□62 to 2□16) p=0□81	1□15 (0□62 to 2□13) p=0□80	0□97 (0□39 to 2□38) p=1□00	0□96 (0□39 to 2□36) p=1□00

Figure 1: Participant flow chart with treatment allocation and exclusions

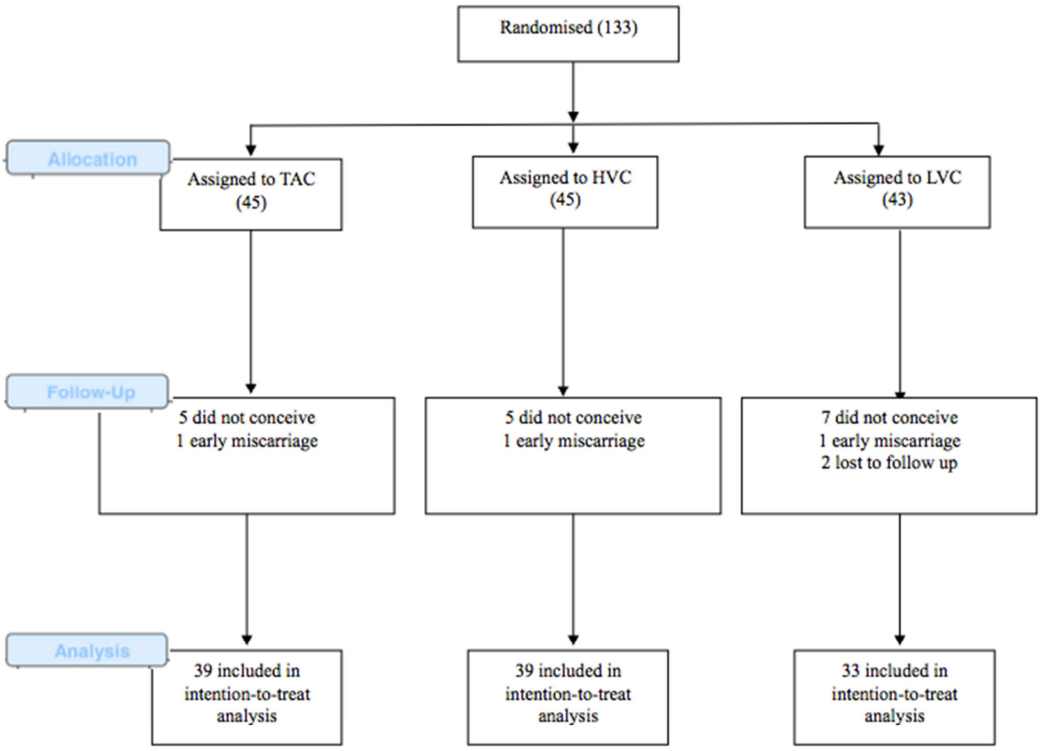


Figure 2: Pregnancy outcome by treatment allocation